REMARKS

The Office Action of February 27, 2002 presents the examination of claims 1-2 and 8-17. Claims 3-7 and 18-25 are withdrawn from consideration. Claims 26-28 are added for the Examiner's consideration. Support for the added claims is found in the specification, particularly on page 8, lines 15-17, and page 14, lines 20-25. No new matter is added to the application.

Election/Restriction

The Examiner maintains the restriction requirement, so that only claims 1, 2, and 8-17, which read upon the elected species of "X": GLY-GLY-GLY-PRO-GLY-LYS-ARG, were examined in the instant Office Action. Applicants respectfully request that the Examiner rejoin the non-elected claims once allowable generic or linking claims have been found.

Priority

The Examiner objects to the Oath/Declaration for not making reference to the priority document KR 2000-58003. In response to the Examiner's remarks, Applicants are in the process of obtaining an executed Supplemental Declaration referencing priority to KR 2000-58003, and will file the Supplemental Declaration in good time. Applicants note that priority is based on the foreign application since KR 2000-58003 was filed on October 2, **2000** and the present invention was filed only five weeks later on November 7, **2000**. Thus, contrary to the Examiner's assertions, the present application was not filed more than a

year after the filing of the priority document, and priority on KR 2000-58003 is appropriate.

Drawings

The Examiner notes that formal drawings will be required when the application is allowed. Applicants will file formal drawings at that time.

Specification

The Examiner objects to the specification for various informalities. Applicants respectfully traverse. Reconsideration and withdrawal of the instant objection are respectfully requested.

First, the Examiner asserts that the title is not descriptive and suggests the following new title: --A SINGLE-CHAIN INSULIN ANALOG AND A POLYNUCLEOTIDE SEQUENCE ENCODING THE ANALOG--. In response to the Examiner's remarks, Applicants amend the title accordingly.

Second, the Examiner points out that the specification refers to Table 1, which was not filed with the application. In response to the Examiner's remarks, Applicants delete all references to Table 1 in the specification.

Applicants respectfully submit that the above amendments overcome the Examiner's objection to the specification. Withdrawal of the instant objection is respectfully requested.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejects claims 1-2 and 8-17 under 35 U.S.C. § 112, first paragraph for an alleged lack of enablement. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are respectfully requested.

Specifically, the Examiner acknowledges that the specification provides enablement for a single-chain insulin analog compound of formula (I) wherein the joining peptide is SEQ ID NO:1, but asserts that the specification does not provide enablement for a single-chain insulin analog compound of formula I wherein the joining peptide is *any peptide of 5 to 18 amino acids*.

Applicants respectfully disagree with the Examiner's assertions. The creation of a peptide of between 5 and 18 amino acids would not cause the skilled artisan undue experimentation. As disclosed in the instant specification, the exact amino acids which make up the linker are not critical, as long as the amino acids do not cause the SIA (single-chain nucleotide analog) to form hexamers.

In support of her argument, the Examiner points to an article by Wells (*Biochemistry* (1990) 29:8509-8517) and Ngo et al., *The Protein Folding Problem and Tertiary Structure Prediction*, pp. 492-495), both of which describe the modulation of protein function by mutation. However, these articles describe changes in *protein function*, such as catalytic activity. For example, Wells states that protein function may be modified

when sites of mutations strongly interact with one another (i.e. through direct contact or via electrostatic interactions) or function cooperatively (i.e. for a catalytic triad). See, conclusions, page 8515. These articles do not address a linker peptide, which by definition does not encode a functional protein *per se*, but rather is used as a bridge structure to link two peptide chains together, providing the structural conformation necessary for the SIA to uptake glucose and bind the insulin receptor. For these reasons, the references relied upon by the Examiner are not applicable to the instant claims.

The Examiner also asserts that the specification does not provide the skilled artisan with any guidance about which linkers to choose. Applicants strongly disagree with the Examiner on this point. The specification discloses that the linker has the formula U_1-Z_n-Y_m-Z_1-U_n with specific limitations thereon, which is recited in claim 3. The specification also discloses 10 specific examples of acceptable linkers, i.e. SEQ ID NOs: 1-2 and 4-11, now recited in claims 26-28. Thus, given the small number of possible linkers and the large number of specific examples provided in the specification, Applicants respectfully submit that it would *not* be undue experimentation for one skilled in the art to make and use a linker of between 5 to 18 amino acids.

Further, the Examiner asserts that while the specification enables a polynucleotide comprising SEQ ID NO:3, the specification allegedly does not enable *any polynucleotide* encoding a single-chain insulin analog (SIA). Applicants respectfully disagree. First, the insulin A and B chains are

known in the art. The insulin A and B chains may be modified in length, sequence etc. As described in the specification on page 7, line 29 to page 8, line 5, there are several recombinant insulin analogs known in the art that are modified in length or sequence of the insulin A and B chains. As evidence thereof, Applicants submit six journal articles (BREMS et al., Altering the association properties of insulin by amino acid replacement, Protein Engineering, vol. 5, no. 6, pp, 527-533; SCHWARTZ et al., A superactive insulin: [B10-Aspartic acid]insulin(human), Proc. Natl. Acad. Sci. USA, vol. 84, pp. 6408-6411, September 1987; BRANGE et al., Monomeric insulins obtained by protein engineering and their medical implications, Nature, vol. 333, June 1988, pp. 679-682; GOEDDEL et al., Expression in *Escherichia coli* of chemically synthesized genes for human insulin, Proc. Natl. Acad. Sci. USA, vol. 76, no. 1, pp. 106-110, January 1979; THIM et al., Secretion and processing of insulin precursors in yeast, Proc. Natl. Acad. Sci. USA, vol. 83, pp. 6766-6770, September 1986; and MARKUSSEN et al., Soluble, prolonged-acting insulin derivatives, Protein Engineering, vol. 2, no. 2, pp. 157-166, 1988) evidencing that it would not be undue experimentation to create variants of the A and B chains. The Examiner is reminded that an application need not include, and preferably omits, what is already known in the art. In re Buchner 929 F.2d 660 (Fed. Cir. 1991).

It appears that the Examiner's rejection turns on the combination of the A chain, X, and the B chain. However, as explained above, it would be undue experimentation to create a linker peptide. Further, since A and B chain variants are known

in the art, the combination of all three elements (A chain, X, and the B chain) is clearly within the bounds of routine experimentation for one of ordinary skill in the art, given the guidance present in the specification.

For all of the above reasons, Applicants respectfully submit that the instant claims fully comply with 35 U.S.C. § 112, first paragraph. Withdrawal of the instant rejection is respectfully requested.

Summary

Applicants respectfully submit that the above amendments and remarks address and overcome all of the Examiner's rejections of record. Therefore, all of the present claims define patentable subject matter such that this application should be placed into condition for allowance. Early and favorable action of the merits of the present application is thereby respectfully requested.

If there are any minor matters precluding allowance of the application which may be resolved by a telephone discussion, the Examiner is respectfully requested to contact Kristi L. Rupert, Ph.D. (Reg. No. 45,702) at (703) 205-8000.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional

fees required under 37 C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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JWB/KLR/gml
Attachment: Version with Markings to Show Changes Made

BREMS et al., Altering the association properties of insulin by amino acid replacement, Protein Engineering, vol. 5, no. 6, pp, 527-533;

SCHWARTZ et al., A superactive insulin: [B10-Aspartic acid]insulin(human), Proc. Natl. Acad. Sci. USA, vol. 84, pp. 6408-6411, September 1987;

BRANGE et al., Monomeric insulins obtained by protein engineering and their medical implications, Nature, vol. 333, June 1988, pp. 679-682;

GOEDDEL et al., Expression in *Escherichia coli* of chemically synthesized genes for human insulin, Proc. Natl. Acad. Sci. USA, vol. 76, no. 1, pp. 106-110, January 1979;

THIM et al., Secretion and processing of insulin precursors in yeast, Proc. Natl. Acad. Sci. USA, vol. 83, pp. 6766-6770, September 1986;

MARKUSSEN et al., Soluble, prolonged-acting insulin derivatives, Protein Engineering, vol. 2, no. 2, pp. 157-166, 1988.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

The title has been amended as follows:

[TREATMENT OF DIABETES USING SINGLE CHAIN INSULIN ANALOG]

--A SINGLE-CHAIN INSULIN ANALOG AND A POLYNUCLEOTIDE SEQUENCE ENCODING THE ANALOG--.

The paragraph beginning on page 20, line 13, has been amended as follows:

First, the inventors generated a single-chain insulin analog (SIA-1) by replacing 35 residues of the C-peptide with a short turn-forming heptapeptide (Gly-Gly-Gly-Pro-Gly-Lys-Arg). The inventors produced recombinant SIA-1 in *Escherichia coli*, refolded it, and examined its biological activity using receptor binding and glucose uptake assays. The inventors found that the receptor binding activity of SIA-1 was 12-fold higher than that of proinsulin and 3- to 4-fold lower than that of insulin. Similarly, the glucose uptake activity of SIA-1 was 16-fold higher than that of proinsulin and 4- to 5-fold lower than that of insulin [(Table 1)]. To determine whether SIA has a sufficient capability to control blood glucose in animals, as does insulin, the inventors administered SIA to 8 week-old Sprague-Dawley (SD) rats and determined the concentration of glucose in the whole blood. The inventors found that the hypoglycemic effect of SIA was 2- to 3-fold higher than that of proinsulin and 2-fold lower than that of insulin [(Table 1)]. This result indicates that the

biological activity of the recombinant SIA is somewhat comparable to that of insulin.

IN THE CLAIMS:

Claims 26-28 have been added.